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10/591,883	12/10/2007	Maurice S. Swanson	60677US(49163)	3251

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,883	SWANSON ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-13 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-13 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment and Remarks, filed 8/14/09, have been entered. Claim 1 is amended; claims 2, 3, and 14-29 are cancelled; claims 30-32 are newly added; claims 1, 4-13, 30-32 are pending and under current examination.

Election/Restrictions

Applicant's election of Group I (claims 1-13) in the reply filed on 4/15/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 14-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Groups, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/15/09.

Specification

The objection to the disclosure is withdrawn in view of Applicants' amendment to the specification to delete the embedded hyperlink.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-13, 30-32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

1) A method of reducing **myotonia** in the muscle of an individual suffering from myotonia, comprising *intramuscular injection* of a recombinant adeno-associated viral (rAAV) vector comprising a promoter operably linked to a nucleic acid encoding muscleblind1 (MBNL1) protein, wherein expression of the MBNL1 protein results in reducing **myotonia** in the muscle of the individual.

2) A pharmaceutical composition comprising a recombinant adeno-associated viral (rAAV) ***vector*** comprising *a promoter operably linked* to a nucleic acid encoding muscleblind 1 (MBNL1) protein.

The specification does not reasonably provide enablement for

1) Any mode of administration of the rAAV.

2) Utilizing any combination of transgenes encoding for MBNL1, MBNL2, MBNL3.

3) The reversing of mis-splicing of variously claimed proteins *in vivo*.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants have now amended the claims with regard to the specific disease to be treated (myotonic dystrophia), an rAAV vector to be used. Thus, Applicants' amendments are found to be persuasive with regard to these particular aspects of the prior rejection of record. However, Applicants' amendments have not overcome #1-#3 detailed above.

Applicants' Arguments. Applicants argue that rAAV vectors have been used for successful expression of a number of genes *in vitro*, as detailed in the specification. Applicants point out that the present invention does teach a particular vector, rAAV, for gene expression, and does teach intramuscular injection of the rAAV construct into a transgenic mouse for DM. Applicants point to Example 4 of the as-filed disclosure. See pages 8-9 of the Response. Applicants argue that the art cited by the Examiner (Juengst, Kay, Gregorovic) are 6-8 years old, and the field of gene therapy has changed considerably in this time. Applicants point to Stedman (2000) that show a Phase I clinical trial was conducted using gene therapy for limb girdle muscular dystrophy, and Clemens (2009). Applicants argue that the specification provides enablement for using an rAAV vector in the claimed methods. See pages 9-10 of the Response.

Response to Arguments. These arguments have been fully considered but are not persuasive. In particular, the prior rejection cites Juengst, Kay, Gregorovic to provide evidence to show that there is a lack of predictability in the art with regard to the amount of therapeutic protein produced, the mode of administration of the nucleic acid, the specific targeting of specific tissues and/or cells, and with regard to a specific therapeutic outcome. In view of this unpredictability, the Examiner provides the scope of enablement, detailed above, which clearly teaches that Applicants have enabled using a particular protein (MBNL1), by a particular mode of administration (intramuscular) in order to achieve a particular effect (reduction of myotonia). It is noted that the effective filing date of the as-filed disclosure is 3/10/04, which is reasonably represented by the state of the art detailed by the cited art. The MPEP makes clear that enablement must be determined at the time of filing. See also, MPEP §2164.05 states that: To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a

declaration after the filing date which demonstrates that the claimed invention works. However, the examiner should carefully compare the steps, materials, and conditions used in the experiments of the declaration with those disclosed in the application to make sure that they are commensurate in scope; i.e., that the experiments used the guidance in the specification as filed and what was well known to one of skill in the art. Such a showing also must be commensurate with the scope of the claimed invention, i.e., must bear a reasonable correlation to the scope of the claimed invention.

Applicants have provided Clemens as support for enablement of the claimed invention. It is noted that Clemens is not within the scope of the claimed invention because they are discussing a different diseases than the instantly claimed invention (muscular dystrophy (p. 2), hemophilia B (p. 3) not myotonic dystrophia); different genes (SGCA (p. 2); factor IX (p. 3)). Applicants have not overcome the *prima facie* case of lack of enablement because the steps, materials, conditions used in the cited art of Clemens is not within the scope of the claimed invention, and therefore does not provide enablement for the aspects of delivery of the rAAV vector by any method of administration, or to utilize any protein selected from the group consisting of MBNL1, MBNL2 and MBNL3.

Applicants' Arguments. Applicants further argue that, with regard to the mode of administration, the art recognizes that it can be administered by many methods, and point to the specification, page 12, line 28, that successfully transduced rAAV vectors include T-lymphocytes, B-lymphocytes, etc. and that the rAAV vectors can be administered intravenously, parenterally or intraperiotoneally. Applicants point to Example 4, which shoes injection into the left tibialis anterior muscle of mice which shows a reduction in myotonia. Applicants argue that this shows enablement for administering the rAAV in the claimed methods. See page 10 of the Response.

Response to Arguments. These arguments have been fully considered, but are not persuasive. In particular, p. 12, line 28 discusses transduction of various other cell types, but does not provide enablement for providing an rAAV vector comprising a nucleic acid encoding a protein selected from MBNL1, MBNL2, or MBNL3 by any means of administration. There is no guidance as to how these other cells were targeted, or how targeting these cells would provide a nexus for expression of the claimed proteins, such that expression of the protein results in reducing myotonia in a subject. That is, there is no guidance, other than by intramuscular injection, that injection of an rAAV vector comprising a nucleic acid encoding a protein selected from MBNL1, MBNL2, or MBNL3 would, without undue experimentation, result in reduction of myotonia. The state of the art provides clear guidance to show the unpredictability in the art, with regard to the particular mode of administration for a gene therapy vector. Neither Applicants' arguments nor the art or record provide any guidance to enable utilizing an rAAV vector in the claimed methods to arrive at the claimed result using any mode of administration of the vector.

Applicants' Arguments. Applicants argue that the specification provides guidance and support for treating myotonic dystrophia by administering a rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL2 or MBNL3 protein. Applicants argue that muscleblind-like (MBNL) proteins and CUG-BP1 and ETR-3-like factors (CELF) are implicated in the pathogenesis of myotonic dystrophy type 1 (DM1). Applicants argue that MBNL1, 2, and 3 all regulate splicing of mRNA targets known to be abnormally regulated in DM. Applicants further argue that the specification teaches on page 32, line 34 to test whether the MBNL family can also regulate human IR, the three MBNL family members were co-expressed with the human IR minigene, and that in contrast to an inhibitory effect of MBNL on cTNT splicing, this co-expression strongly induced exon inclusion. Applicants cite Ho *et al.* who show that all three MBNL family

members are novel splicing regulators that act antagonistically to CELF proteins. Thus, Applicants argue that the claims are enabled for the breadth of all three MBNL proteins. See pages 11-12 of the Response.

Response to Arguments. These arguments have been considered, but are not persuasive. The arguments only provide guidance in showing that the three MBNL proteins regulate splicing and are implicated in the pathogenesis of DM1. However, these arguments and cited art do not provide an enabling disclosure to show that using an rAAV vector encoding any of the three MBNL proteins, would result in the therapeutic result of reducing myotonia. In particular, one of skill in the art could not rely upon the state of the art to predict that any one of these proteins, other than MBNL1, would result in reduction of myotonia. The fact that these proteins are related fails to provide guidance to show how they would all result in the same therapeutic outcome, of reduction of myotonia. The art at the time of filing clearly shows the unpredictability in gene therapy, particularly, with regard to the particular gene that is used.

The working examples that pertain to claims 4-8 are *in vitro* examples, with cell types that are not necessarily representative of cells that are isolated from a mammal suffering from an aberrant microsatellite expansion disease. For example, the specification uses primary chicken skeletal muscle cells (Example 5), which are made to express human and chicken cTNT and human IR minigenes; however, these cells are not isolated from a mammal that has an aberrant microsatellite expansion disease, therefore it is unclear what nexus can be concluded from these *in vitro* results and a method of treating an aberrant microsatellite expansion disease *in vivo*. The lack of guidance provided by the specification with regard to a correlation between the *in vitro* results and a therapeutic *in vivo* outcome is not considered to be predictable, particularly in light of the unpredictable state of the art of gene therapy. Therefore, it would have required the skilled artisan to practice undue experimentation in order to practice the embodiments of claims 4-8.

Applicants' Arguments. Regarding claims 4-8, Applicants point to Example 4, stating that in mice that were intramuscularly injected with an rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1 protein, the levels of abnormal splicing products were decreased, while the level of normal splicing products was increase (p. 13 of the Response). Applicants further point to example 5, wherein Western blot analysis showed that GFP-MBNL1, 2, and 3 strongly repressed inclusion of both human and chicken cTNT exon 5 in primary chicken skeletal muscle cultures, while expression of GFP to levels comparable to, or greater than, GFP-MBNL fusion proteins had no effect on splicing. See p.1 3 of the Response.

Response to Arguments. These arguments are considered but not persuasive. In particular, the specification provides no specific guidance to show that administration of an rAAV vector containing a transgene encoding either MBNL1, MBNL2, or MBNL3, would result in reversing of the mis-splicing of these proteins. The term "reversing" implies that the proteins would be correctly spliced once they were already produced (*i.e.,* correcting a mis-spliced protein after the protein had already been produced). The specification provides no guidance to show that this would occur *in vivo*, nor does the specification provide guidance to show that the expression of any of the MBNL genes reverses mis-splicing. The working examples, at most, are *in vitro* examples which show the decrease of abnormal splicing products, but not an indication that a fully produced protein that had been mis-spliced was then reversed upon the expression of MBNL proteins.

With regard to claim 12, the claim recites a pharmaceutical composition comprising a rAAV (not an rAAV vector). The specification provides no specific guidance as to how a rAAV would be used in the context of the invention, and how a virus would contain the transgene that encodes for a protein. Accordingly, this aspect of the prior rejection is maintained.

With regard to Applicants' claims, which now recite treating myotonic dystrophia in a subject, the claims are not enabled for this breadth. As discussed previously, the state of the art of gene therapy is unpredictable, with regard to the particular therapeutic outcome, using a particular vector encoding a particular protein, and a particular mode of administration. In the instant case, the specification teaches a specific therapeutic outcome, the reduction of myotonia (see also, enabled scope and Example 4). The working examples of the specification teach that intramuscular injection of a rAAV vector comprising a promoter operably linked to a nucleic acid encoding MBNL1, whereby the expression of MBNL1 causes a reduction of myotonia. Treatment and reduction of myotonic dystrophia encompasses treatment or reduction of other symptoms that are not taught in the specification. For example, the specification teaches that myotonic dystrophy type 1 is characterized by myotonia, or delayed muscle relaxation. However, the specification further teaches that, "Manifestations of DM may also include heart block, ocular cataracts, hypognoadism and nervous system dysfunction." See p. 3, lines 6-9. The specification provides no guidance in showing that using the claimed methods would result in a therapeutic outcome of treating or reducing all the manifestations of DM. The specification only provides guidance to show the reduction of myotonia. The state of the art provides support to show that one of skill in the art could not predictably arrive at a therapeutic result. Accordingly, the scope of enablement has been limited to reduction of myotonia.

Accordingly, in view of the unpredictable state of the art of gene therapy, in particular, muscular gene therapy, with respect to the efficiency of gene transfer, protein expression, producing a therapeutic effect, the lack of specific teachings or guidance provided by the specification, specific guidance for any aspect of treatment, other than reduction of myotonia in muscle tissue, the lack of guidance of any mode of administration of the rAAV vector, other than intramuscular injection, the lack of any nexus between *in vitro* results regarding reversal of mis-

splicing of variously claimed proteins and an *in vivo,* therapeutic result, it would have required undue experimentation for the skilled artisan to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-13 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Synder *et al.* (**Human Gene Therapy**, 8: 1891-1900, November 1997) when taken with Miller *et al.* (**EMBO J.**, 19: 4439-4448, 2000, IDS) as evidenced by the Uniprot website "MBNL1" accessed online on May 10, 2009.

Applicants' Arguments. Applicants argue that Synder does not teach using an rAAV vector containing a transgene encoding MBNL1 because Synder teach a recombinant rAAV vector. Applicants argue that Miller do not cure the defects in the Synder reference because Miller does not teach or suggest a pharmaceutical

composition comprising a rAAV containing a transgene that encodes MBNL1. Apps argue that Miller does not teach MBNL1, 2, or 3, or that any of these would be useful in a pharmaceutical composition for administration (pages 13-14 of the Response).

Response To Arguments. These arguments have been considered but are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In particular Synder provide guidance for utilizing an rAAV vector gene transfer into muscle fibers. Miller (as evidenced by the Uniprot website) teaches MBNL1. The Examiner asserts that it would have been *prima facie* obvious to modify the teachings of Sydner to produce an rAAV vector containing a transgene that encodes MBNL1, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to test the ability of the rAAV vector to express MBNL1, to study MBNL1 over-expression in vivo. One of ordinary skill would recognize that rAAV vectors provide an efficient means to stably transduce muscle fibers.

Rejection

Synder teach utilizing a recombinant rAAV vector for gene transfer into adult immunocompetent mice and teach that AAV vectors efficiently and stably transduce post-mitotic muscle fibers and myoblasts in vivo. See abstract.

However, Synder do not specifically teach that the rAAV vector contains a transgene that encodes for MBNL1. However, prior to the time of the invention, Miller teach the sequence of MBNL1 (the Uniprot website is provided as evidence, see p. 4, References). Miller teach that MBNL1 is expressed in muscle tissue.

Accordingly, it would have been obvious to the skilled art to modify the teachings of Synder to produce an rAAV vector containing a transgene that encoded MBNL1, with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to make this modification to test the ability of the rAAV vector to express MBNL1, to study MBNL1 over-expression in vivo. One of ordinary skill would recognize that rAAV vectors provide an efficient means to stably transduce muscle fibers.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632